

Problems with the calculations in the JAMA Clinical Evidence Synopsis “Oral Zinc for the Common Cold” by Das and Singh (2014)

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This is a comment on:

Das RR, Singh M. Oral zinc for the common cold [JAMA Clinical Evidence Synopsis].

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<http://www.ncbi.nlm.nih.gov/pubmed/24715076>

<http://dx.doi.org/10.1001/jama.2014.1404>

The above JAMA Clinical Evidence Synopsis by Das and Singh (2014) is based on:

Singh M, Das RR. Zinc for the common cold. Cochrane Database Syst Rev 2013, CD001364.

<http://www.ncbi.nlm.nih.gov/pubmed/23775705>

Concerns have been expressed about unattributed copying of text and data,
and about numerous other problems in the above mentioned
Cochrane review by Singh and Das (2013),
see:

<http://hdl.handle.net/10138/153180>

<http://dx.doi.org/10.13140/2.1.1887.3127>

Hereafter the JAMA Clinical Evidence Synopsis by Das and Singh (2014)
is briefly referred to as:

Das and Singh (2014) or
the JAMA Synopsis

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1. Table in the JAMA Clinical Evidence Synopsis by Das and Singh (2014)

The JAMA Clinical Evidence Synopsis “Oral zinc for the common cold” by Das and Singh (2014) is based on the Cochrane review “Zinc for the common cold” by Singh and Das (2013).

The Cochrane review by Singh and Das (2013) is restricted to “double-blind, placebo-controlled randomised controlled trials” (p. 7, Singh and Das 2013). The JAMA Clinical Evidence Synopsis consistently states in the section “Evidence Profile” that the “No. of randomized clinical trials: 14 therapeutic (lozenges: low-dose = 5, high-dose = 7; syrup = 2) among adults (13 trials) and children (1 trial) and 2 prophylactic trials among children only (syrup = 1, tablet = 1)” and these studies are included as “Comparison: Placebo” (p. 1440, Das and Singh 2014). This description implies that the findings presented in the JAMA Synopsis are also based on placebo-controlled randomized studies.

The main findings of the Cochrane review by Singh and Das (2013) are shown in a single Table in the JAMA Clinical Evidence Synopsis by Das and Singh (2014, p. 1441). The part of the Table that describes findings on the effect of zinc on the “duration of colds” is copied at the foot of this page, see below.

Most of the figures in this Table published in the JAMA Synopsis are not directly extracted from the Cochrane review by Singh and Das (2013) and the origin of the figures is not clear. The purpose of this document is to trace the origin of the figures in the Table, and to reproduce the calculations, in order to assess the validity of the reported findings in the Table in Das and Singh (2014).

The Table in the JAMA Synopsis by Das and Singh (2014, p. 1441)

Table. Duration, Severity, and Incidence of Cold for Zinc vs Placebo

Outcome	Comparison	No. of Studies	Total No. of Participants	Mean (SD)		Mean Difference (95% CI) ^a
				Intervention	Control	
Therapeutic studies						
Duration of cold, d	Zinc lozenges vs placebo	12 (11 adults, 1 children)	1342	6.75 (2.36)	7.5 (4.03)	−1.04 (−2.02 to −0.05)
	Zinc syrup vs placebo	2 (children)	314	5.1 (0.4)	5.9 (0.6)	−0.63 (−0.84 to −0.43)
	High dose (≥75mg/d) vs low dose (<75mg/d) zinc lozenges	5 (adults)	543	4.47 (0.52)	8.68 (1.9)	−3.43 (−3.9 to −2.95)

2. Calculation of the difference in the effect between “High dose ($\geq 75\text{mg/d}$) vs low dose ($< 75\text{mg/d}$) zinc lozenges”

On the third row of the Table (see p. 3), Das and Singh (2014) reported that in 5 studies with 543 participants, the means of the duration of colds were as follows:

4.47 days (SD 0.52) in the high zinc dose groups, and
8.68 days (SD 1.9) in the low zinc dose groups.

In the Table, the difference in cold duration between the high vs low dose zinc lozenge groups was reported as:

“ -3.43 (-3.9 to -2.95)” days.

These findings are also repeated in the text section:

“The mean duration of the common cold was 4.47 days in high-dose users ($\geq 75\text{ mg/d}$) and 8.68 days in low-dose users ($< 75\text{ mg/d}$; mean difference, -3.43 [95% CI, -3.9 to -2.95])” (p. 1440).

It is not evident in the JAMA Synopsis, where the data for the “high dose vs low dose” comparison originated. The JAMA Synopsis is based on the Cochrane review by Singh and Das (2013), but that review does not include any comparison of 5 studies with 2 different dosage levels of zinc.

Furthermore, so far only one publication has reported a randomized comparison between high and low zinc doses. The Turner (2000) study had 4 study arms: 1 arm was administered $> 75\text{ mg/day}$ of zinc, 2 arms were administered $< 75\text{ mg/day}$, and 1 arm was the placebo group. There are no other studies with separate study arms that cover different doses of zinc. Thus, there does not appear to be 5 randomized studies that have compared high dose vs low dose of zinc as zinc lozenges.

I examined the Cochrane review by Singh and Das (2013) to ascertain where the data for the “high dose vs low dose zinc lozenges” comparison originates and whether the calculations leading to the reported values can be reproduced.

The above data reported in the JAMA Synopsis can be traced to Analysis 1.2 in the Cochrane review by Singh and Das (2013, p. 51). Subgroup 1.2.1 contains 7 high dose ($> 75\text{ mg/day}$) zinc lozenge studies and subgroup 1.2.2 contains 5 low dose ($< 75\text{ mg/day}$) zinc lozenge studies. In total, the zinc groups of these 12 studies had 668 ($= 311 + 357$) participants, see p. 6 of this document.

In the Table published in the JAMA Synopsis, Das and Singh (2014) report that the number of participants in the 5 studies was 543 (see the Table on p. 3). The difference between the zinc lozenge groups published in Singh and Das (2013) and in Das and Singh (2014) is 125 participants ($668 - 543 = 125$). The same value appears as the sum of the 2 lowest listed high dose zinc lozenge groups ($57 + 68$); i.e. Smith (1989) and Turner (2000) in the subgroup 1.2.1 (high zinc), see p. 6. Thus, the zinc groups of the top 5 studies with high-dose zinc and all the 5 studies with low-dose zinc in Analysis 1.2 combined equal the number of participants that is reported on the third row of the Table of the JAMA Synopsis (i.e. $N = 543$).

Thereafter I examined whether the means and SDs reported in the JAMA synopsis could be reproduced from these 2 sets of 5 zinc groups, see pp. 6-7.

The unweighed mean duration of colds for the 5 high dose studies shown within the red rectangles on p. 6 is 4.47 days, and for the 5 low dose studies shown within red rectangles is 8.68 days, see the calculations on p. 7 of this document. Both of these figures are identical with the mean durations of colds published in the JAMA Synopsis, compare them with the Table on p. 3.

The standard deviations (SDs) calculated from the 5 means within the 2 rectangles are 0.52 days and 1.9 days, see p. 7. They are also identical with the SDs published in the JAMA Synopsis, compare them with the Table on p. 3.

Finally, the JAMA Synopsis reported that the difference between the high zinc dose and low zinc dose studies was -3.43 (95% CI: -3.9 to -2.95) days (see the Table on p. 3). This estimate and its 95% CI can be reproduced by including the 5 high dose and 5 low dose zinc groups as pairs in the same order as they were published in Analysis 1.2 of the Cochrane review by Singh and Das (2013), see p. 8 of this document for the forest plot. Compare the order of values under Mean, SD and Total on the right-hand side (“low zinc”) of the meta-analysis with the order of the 5 zinc groups in the low dose studies in Analysis 1.2.2, see p. 6 of this document.

Thus, Das and Singh (2014) do not give any explanations in the JAMA synopsis as to how they calculated the figures that they reported on the third row of their Table (p. 1441, Das and Singh 2014). The figures do not originate directly or exclusively from their Cochrane review (Singh and Das 2013). Nevertheless, the origin of the figures for the “high dose vs low dose zinc lozenges” comparison can be traced and the calculations for the mean (SD) duration of colds and the estimate of effect and its 95% CI can be reproduced as shown above.

It is highly unlikely that some other combination of the high dose and low dose zinc lozenge groups would be consistent with the statement of “No. of studies: 5” and would lead to the same number of participants, the same mean (SD) values in low and high dose groups, and with the accuracy to two decimal places to the same estimate of difference and its 95% CI limits, as the selection and pairing of the zinc groups described above, and shown on pp. 7-8. Thus, the calculations on p. 7 and the meta-analysis on p. 8 seem to reproduce the analysis that is behind the figures that are reported on the third line of the Table in the JAMA Synopsis, see p. 3.

Analysis 1.2 in the Cochrane review “zinc for the common cold” by Singh and Das (2013, p. 51).

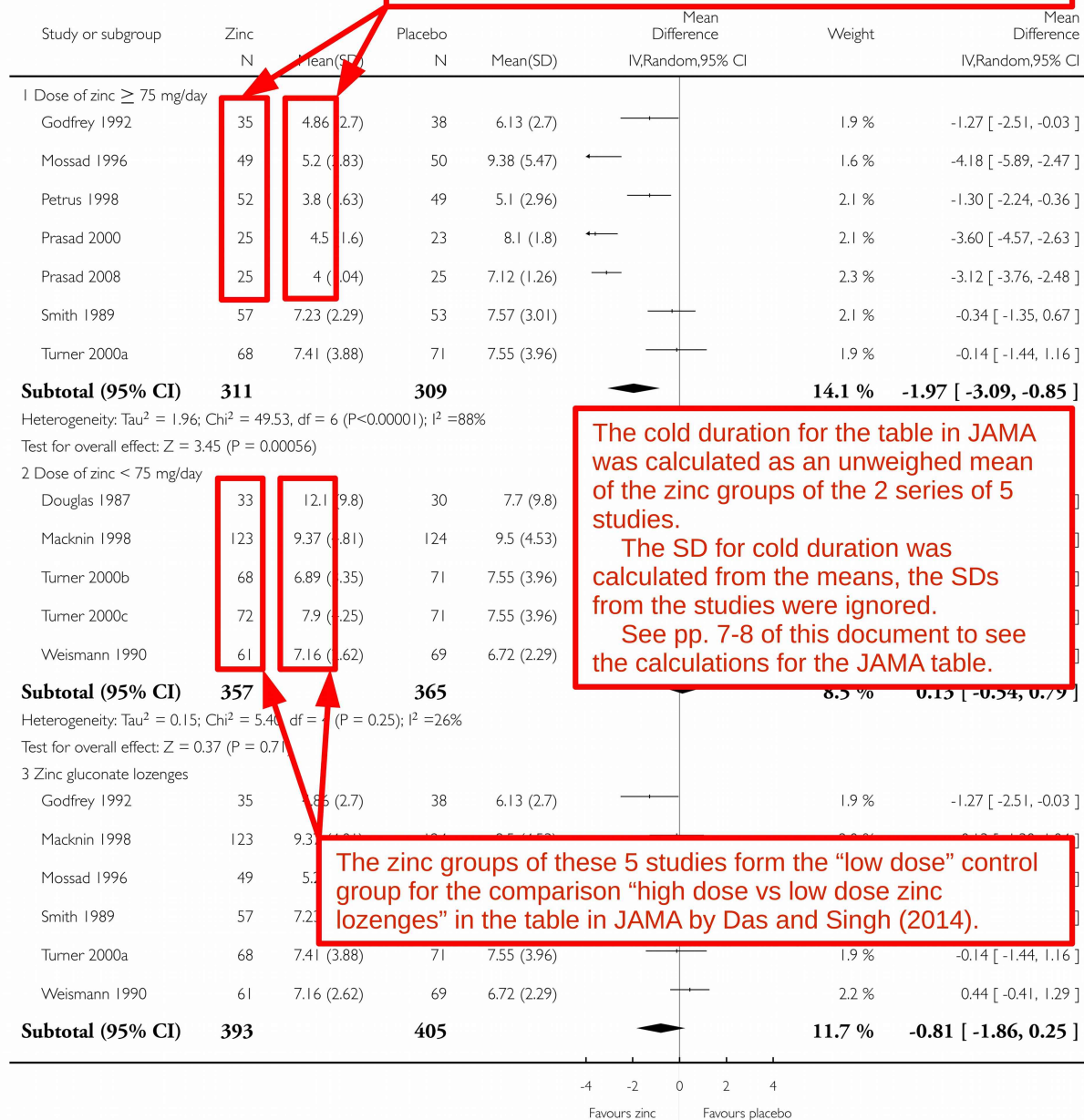
Analysis 1.2. Comparison 1 Zinc versus placebo, Outcome 2 Subgroup analysis (duration of cold symptoms).

Review: Zinc for the common cold

Comparison: 1 Zinc versus placebo

Outcome: 2 Subgroup analysis (duration of cold symptoms)

The zinc groups of these 5 studies form the “high dose” group for the comparison “high dose vs low dose zinc lozenges” in the table in JAMA by Das and Singh (2014).



The cold duration for the table in JAMA was calculated as an unweighed mean of the zinc groups of the 2 series of 5 studies.

The SD for cold duration was calculated from the means, the SDs from the studies were ignored.

See pp. 7-8 of this document to see the calculations for the JAMA table.

The zinc groups of these 5 studies form the “low dose” control group for the comparison “high dose vs low dose zinc lozenges” in the table in JAMA by Das and Singh (2014).

Calculation of the mean and SD from the means reported in Analysis 1.2 of the Cochrane review “zinc for the common cold” by Singh and Das (2013)

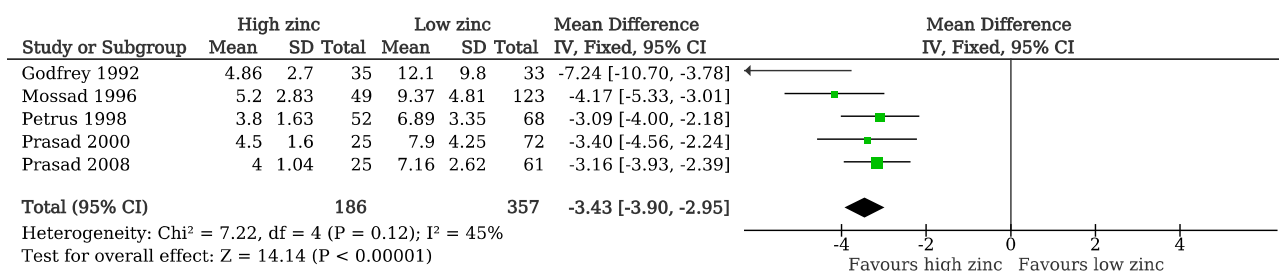
Bold figures indicate the values that are reported in the JAMA Synopsis by Das and Singh (2014).

See the previous page for the copy of Analysis 1.2.

Reproducing the analysis of the difference between “high dose vs low dose zinc lozenges” in the JAMA synopsis by Das and Singh (2014)

Analysis 1.2.1 by Singh and Das (2013)			
High dose (>75 mg/day)	Study	No. of participants	Duration of colds (days)
	Godfrey (1992)	35	4.86
	Mossad (1996)	49	5.2
	Petrus (1998)	52	3.8
	Prasad (2000)	25	4.5
	Prasad (2008)	25	4
Not included:	Smith (1989)		
Not included:	Turner (2000a)		
	Total	186	
	Mean (unweighed)		4.47
	SD (population)		0.521
Analysis 1.2.2 of Singh and Das (2013)			
Low dose (<75 mg/day)	Study		
	Douglas (1987)	33	12.1
	Macknin (1998)	123	9.37
	Turner (2000b)	68	6.89
	Turner (2000c)	72	7.9
	Weismann (1990)	61	7.16
	Total	357	
	Mean (unweighed)		8.68
	SD (population)		1.91
	Overall Total	543	

Meta-analysis reproducing the reported mean difference and its 95% CI in JAMA Synopsis by Das and Singh (2014)



The analysis above was done by Hemilä (2015) to reproduce the estimate of differences and its 95% CI on the third row in the Table of JAMA Synopsis (Das and Singh 2014), see p. 3. The RevMan program was used to calculate the pooled effect and construct the forest plot.

The meta-analysis above is based on the following pairs of zinc groups:

The pairing in the above meta-analysis

“High zinc” – “Low zinc”

Godfrey 1992 – Douglas 1987

Mossad 1996 – Macknin 1998

Petrus 1998 – Turner 2000b

Prasad 2000 – Turner 2000c

Prasad 2008 – Weismann 1990

Some of the differences between the studies

“High zinc” – “Low zinc”

USA (18-40 y) - Australia (mean 33 y)
- lozenge composition, p 10

Adults (21-69 y) - Children (6-16 y)

- lozenge composition, p 10

- lozenge composition, p 10

USA (28-41 y) - Denmark (18-65 y)

The high zinc and low zinc groups above are in the same order as they appeared in Analysis 1.2 of Singh and Das (2013), compare with p. 6 of this document.

The resulting estimate and its 95% CI are identical with that published in the JAMA Synopsis by Das and Singh (2014), compare with the Table on p. 3.

The calculations for the comparison of “high dose vs low dose zinc lozenges” by Das and Singh (2014), described on the previous pages, have serious problems:

A) The JAMA Synopsis by Das and Singh (2014) gives a strong impression to the reader that all the described findings are based on randomized comparisons: “Evidence Profile ... randomized clinical trials” (Das and Singh 2014, p. 1440). However, the comparison of “high dose vs low dose” groups by Das and Singh (2014) is not based on randomized groups, but it is instead based on different zinc groups from different studies with different conditions. There are numerous differences between the paired groups in addition to the zinc dosage, thus it is not reasonable to assume that the dose of zinc is the only difference between the paired high dose and low dose groups. Finally, the only published randomized comparison of different doses of zinc by Turner (2000) is missing from the pairings, see pp. 7-8, although Turner (2000a) is listed as a “high zinc dose” group in Analysis 1.2.1 by Singh and Das (2013), see p. 6.

B) Selection of the 5 high dose zinc studies for the comparisons is arbitrary and biased. Analysis 1.2.1 includes 7 high dose zinc groups. Das and Singh (2014) selected 5 of them, leaving out the 2 high dose zinc groups with the longest durations of the cold, see p. 6. The mean duration of colds in these 2 excluded studies were: 7.23 days (Smith 1989) and 7.41 days (Turner 2000a), see p. 6. The cold durations reported in those 2 studies are 2 days longer than the third longest colds of 5.2 days duration reported in the Mossad (1996) study. Thus, by excluding the Smith (1989) and the Turner (2000a) high dose zinc groups, Das and Singh (2014) bias the estimate of the duration of colds in the high dose zinc lozenge groups (i.e. the 4.47 days) towards shorter cold durations. The estimate of the difference between high dose and low dose groups is simultaneously skewed towards a greater value (i.e. the 3.43 days).

C) The estimated value of the difference between the high dose and low dose groups depends on the order of how the studies are paired in the meta-analysis. The reproduced comparison on p. 8 is based on taking the high zinc and the low zinc groups in the same order as they appear in Analyses 1.2.1 and 1.2.2, compare pp. 6 and 8. These pairings resulted in the difference and its 95% CI published by Das and Singh (2014). However, there is no basis for considering that the high dose zinc group of Godfrey (1992) (USA) is most similar to the low dose zinc group of Douglas (1987) (Australia), or that the high dose zinc group of Mossad (1996) (Adults) is most similar to the low dose zinc group of Macknin (1998) (Children), etc, see p. 8. There is no justification for this particular arbitrary pairing of the 2 sets of 5 zinc groups.

D) When the number of participants varies between 25 and 49 in the high dose studies and between 33 and 123 in the low dose studies (see pp. 6-7), it is not reasonable to pool the results by calculating an unweighed mean duration of the groups. When the overall means are calculated for the 2 sets of 5 zinc groups, the variation in the size of the groups should be taken into account by weighing the individual means.

E) Calculating the SD for the overall mean of the 5 zinc groups from the point estimates of the 5 groups is not the correct approach. The SD for the overall mean should be calculated from the SDs of the 5 groups, and not from the point estimates of the 5 groups (i.e. means).

As stated in comments B) and C) above, the selection of 5 high dose zinc groups out of all the 7 high dose zinc groups is arbitrary, and their pairing with the low dose zinc groups is also arbitrary. If the high dose zinc groups with the shortest duration of colds by Petrus (1998) and Prasad (2008) are replaced by the high dose zinc groups with the longest durations of colds by Smith (1989) and Turner (2000a), and the order of pairing is shuffled, the estimate of “high dose vs low dose zinc lozenge” difference can fall to as low as 1.75 days, which is half of the difference (i.e. 3.43 days) reported by Das and Singh (2014), see p. 11. Thus, the reported estimate of “high dose vs low dose zinc lozenge” difference reported by Das and Singh (2014) is meaningless since it is based on the arbitrary pairing of arbitrarily selected zinc groups from 12 different studies.

Furthermore, in the set of 5 low dose zinc groups, the dose of zinc is not the only relevant issue. The lozenge preparations used in some studies would not be expected to release zinc effectively. Eby (2001) pointed out that the Turner (2000) lozenges contained palm kernel and cotton-seed oils, and at the high temperatures used in the manufacture of these lozenges those ingredients react with zinc ions to make insoluble compounds. The lozenge used by Douglas (1987) contained a high amount of tartaric acid, which binds zinc and therefore free zinc ions are not easily released from such lozenges (Eby 2004, p. 31). The 2 zinc groups reported by Turner (2000) and the 1 zinc group reported by Douglas (1987) cover 3 of the 5 “low dose zinc lozenge” studies. Thus, the lack of effect by zinc in these 3 studies (compared with their respective placebos) might be, at least partly, unrelated to the nominal zinc dosage *per se*, and could instead be caused by the poor solubility of zinc caused by the lozenge formulations. Thus, because of the problems with the lozenge formulations, these 3 studies are not suitable for an analysis of dose response effects of zinc administered as lozenges. Finally, the only trial that has been done with children (6 to 16 y) by Macknin (1998) falls to the low dose group. It is possible that the effect of zinc lozenges is different in children compared with adults, so that the zinc dose cannot be considered as the only relevant issue in that study when compared with the Mossad (1996) study.

As noted on p. 4, the only trial that has administered different doses of zinc to randomized groups was reported by Turner (2000). However, the composition of the lozenges was not satisfactory for the reasons detailed above. Thus, although Turner (2000) is the only study that could provide relevant information of dose response of zinc effects from the clinical trial point of view, that study was limited by the lozenge formulations.

There is strong evidence that a high dose (>75 mg/day) zinc lozenges shorten the duration of colds, but so far there is no evidence that low dose (<75 mg/day) zinc lozenges shorten colds (Hemilä 2011). That limit of 75 mg/day was introduced as a pragmatic cut off limit to visualize the systematic differences between the high and low dosage studies (Hemilä 2011). However, the published low dose studies may also be negative for reasons other than the actual zinc dose used, as pointed out above. For example, we do not know if, say, 50 mg/day of zinc as zinc acetate lozenges might substantially influence the duration of colds if an optimal formulation of lozenges is used.

For the reasons listed above from A) to E), the findings reported on the third row of the Table of the JAMA Synopsis are not valid.

A different selection of “high zinc” groups and a different pairing permutation of the “high zinc” and “low zinc” groups can lead to a mean difference of common cold duration which is half of that reported by Das and Singh (2014)

In the JAMA Synopsis, Das and Singh (2014) reported that:

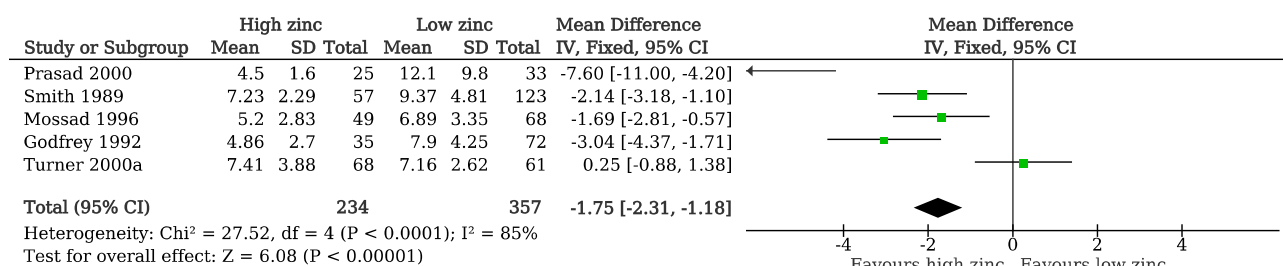
“The mean duration of the common cold was 4.47 days in high-dose users (≥ 75 mg/d) and 8.68 days in low-dose users (< 75 mg/d; mean difference, -3.43 [95% CI, -3.9 to -2.95])” (p. 1440).

The estimate of 3.43 days is based on the exclusion of 2 high dose zinc lozenge groups that reported the longest colds (Smith 1989 and Turner 2000a) and on the pairing of high zinc vs. low zinc groups in the order they were listed in Analysis 1.2, see pp. 6-9.

There is no justification for the particular selection of the 5 uppermost high dose studies in Analysis 1.2.1 by Das and Singh (2014), nor for the specific pairing of the high zinc and low zinc studies by their order on the list.

If the 2 high dose zinc groups with the shortest colds are replaced by the zinc groups of Smith (1989) and Turner (2000a), and the pairing is shuffled, a difference of 1.75 days is reached between the high zinc vs low zinc groups, see the meta-analysis below. In the pairing shown below, the order of the “low zinc” studies is kept the same as in the meta-analysis on p. 8.

This difference of 1.75 days is half of the 3.43 day difference reported in the JAMA synopsis, see p. 3. However, this particular selection of high dose zinc lozenge studies and this pairing is no less applicable than the selection and pairing leading to the 3.43 day difference published by Das and Singh (2014), see p. 8 of this document.



3. Calculating the effect of zinc syrup on the duration of colds

On the second row of the Table, the JAMA Synopsis by Das and Singh (2014) (see p. 3) reported that in 2 zinc syrup studies with 314 participants, the mean duration of colds was:

5.1 days (SD 0.4) in the zinc groups, and

5.9 days (SD 0.6) in the placebo groups.

The difference in cold duration between the syrup and placebo groups was reported as:

“-0.63 (-0.84 to -0.43)” days.

These findings are also repeated in the text section of the JAMA synopsis by Das and Singh (2014) :

“The mean duration was 5.1 days in the syrup group and 5.9 days in the placebo group (mean difference, -0.63 [95% CI, -0.84 to -0.43])” (p. 1440).

I searched for the data used in the Cochrane review by Singh and Das (2013) and figured out how to reproduce the calculations behind the figures published for the 2 zinc syrup studies.

The figures reported on zinc syrup studies in the JAMA Synopsis can be traced to Analysis 1.2.6 in the Cochrane review by Singh and Das (2013, p. 52), see p. 15 for a copy of that analysis.

Two studies by Kurugöl (2006a, 2007) have examined the effect of zinc syrup on common cold duration. The analysis of these studies is reproduced on the next page. The mean durations reported in the Table of the JAMA Synopsis by Das and Singh (2014) are given as unweighed means. Similarly, the SDs are not calculated from the study SDs (the correct way), but they are calculated from the study means (the point estimates; the incorrect way as explained on p. 9).

The effect of zinc syrup was -0.63 (-0.84 to -0.43) days according to the JAMA Synopsis by Das and Singh (2014). According to the Analysis 1.2.6 of the Cochrane review by Singh and Das (2013), the effect of zinc syrup was -0.65 (-0.92 to -0.39) days, see p. 15 of this document. The former value was calculated by the fixed effect model, whereas the latter was calculated using the random effects model, which explains the slight difference.

The presentation of zinc syrup findings suffers from the problems described in D) and E) on p. 9.

**Calculation of the zinc syrup mean and SD reported by Das and Singh (2014)
from the means reported in Analysis 1.2 of Cochrane review
“Zinc for the common cold” by Singh and Das (2013)**

The table below shows the means and SDs for the duration of colds in Singh and Das (2013).
See p. 15 for a copy of Analysis 1.2.6.

The bold numbers indicate the values reported in the JAMA Synopsis by Das and Singh (2014).

**Reproducing the analysis of the effect of zinc syrup on the duration of colds
in the JAMA synopsis by Das and Singh (2014)**

Analysis 1.2.6 in Singh and Das (2013)			
Zinc as syrup	Study	No. of participants	Duration of colds (days)
	Kurugöl (2006a)	97	4.7
	Kurugöl (2007)	60	5.5
	Total	157	
	Mean (unweighed)		5.10
	SD (population)		0.400
Placebo	Study		
	Kurugöl (2006a)	97	5.3
	Kurugöl (2007)	60	6.5
	Total	157	
	Mean (unweighed)		5.90
	SD (population)		0.600
	Overall Total	314	

4. Calculating the effect of zinc lozenges on the duration of colds

On the first row of the Table in the JAMA Synopsis (see p. 3), Das and Singh (2014) reported that in 12 studies with 1342 participants, the mean duration of colds was:

6.75 days (SD 2.36) in the zinc groups, and

7.5 days (SD 4.03) in the placebo groups.

The difference in cold duration between the syrup and placebo groups was reported as:

“-1.04 (-2.02 to -0.05)” days.

The findings are also repeated in the text section:

“The mean duration of cold symptoms was 6.75 days in the lozenge group and 7.5 days in the placebo group (mean difference, -1.04 [95% CI, -2.02 to -0.05)” (p. 1440).

The findings reported on the first row of the Table published in the JAMA Synopsis originates from Analysis 1.2.5 in the Cochrane review by Singh and Das (2013, p. 52), see the next page.

Analysis 1.2.5 of the Cochrane review by Singh and Das (2013) has two serious errors, which were passed directly onto the JAMA Synopsis.

First, Analysis 1.2.5 wrongly states that the duration of colds was 4.4 days in the zinc group of the Petrus (1998) study, whereas Petrus (1998) actually reported that the duration was 3.8 days, see the next page. In 2011, I wrote a Feedback (2011) on the previous version of the Cochrane review by Singh and Das (2011), in which I pointed out that error of data extraction. Despite this, the wrong figure of 4.4 days remained in the updated Cochrane review by Singh and Das (2013), see p. 15. This leads to an incorrect mean duration of colds in the zinc groups reported in the JAMA Synopsis (i.e. 6.75 days is not correct).

Second, Analysis 1.2.5 in Singh and Das (2013) counts the placebo-group of Turner (2000) 3 times. This leads to 142 (= 2 * 71) phantom participants in the placebo column, see p. 15. The correct number of participants in the 12 lozenge studies is therefore not 1342 as stated in the Table of JAMA Synopsis (see p. 3), but it is 1200 participants. The multiple counting introduces an error in the mean duration of colds in the placebo groups (i.e. 7.5 days is not correct) and also leads to misleading accuracy of the Turner (2000) comparisons. The problems of multiple counting of the same participants is briefly commented on in the Cochrane Handbook:

“A serious unit-of-analysis problem arises if the same group of participants is included twice in the same meta-analysis (for example, if ‘Dose 1 vs Placebo’ and ‘Dose 2 vs Placebo’ are both included in the same meta-analysis, with the same placebo patients in both comparisons)” (Higgins 2011, sec 9.3.9).

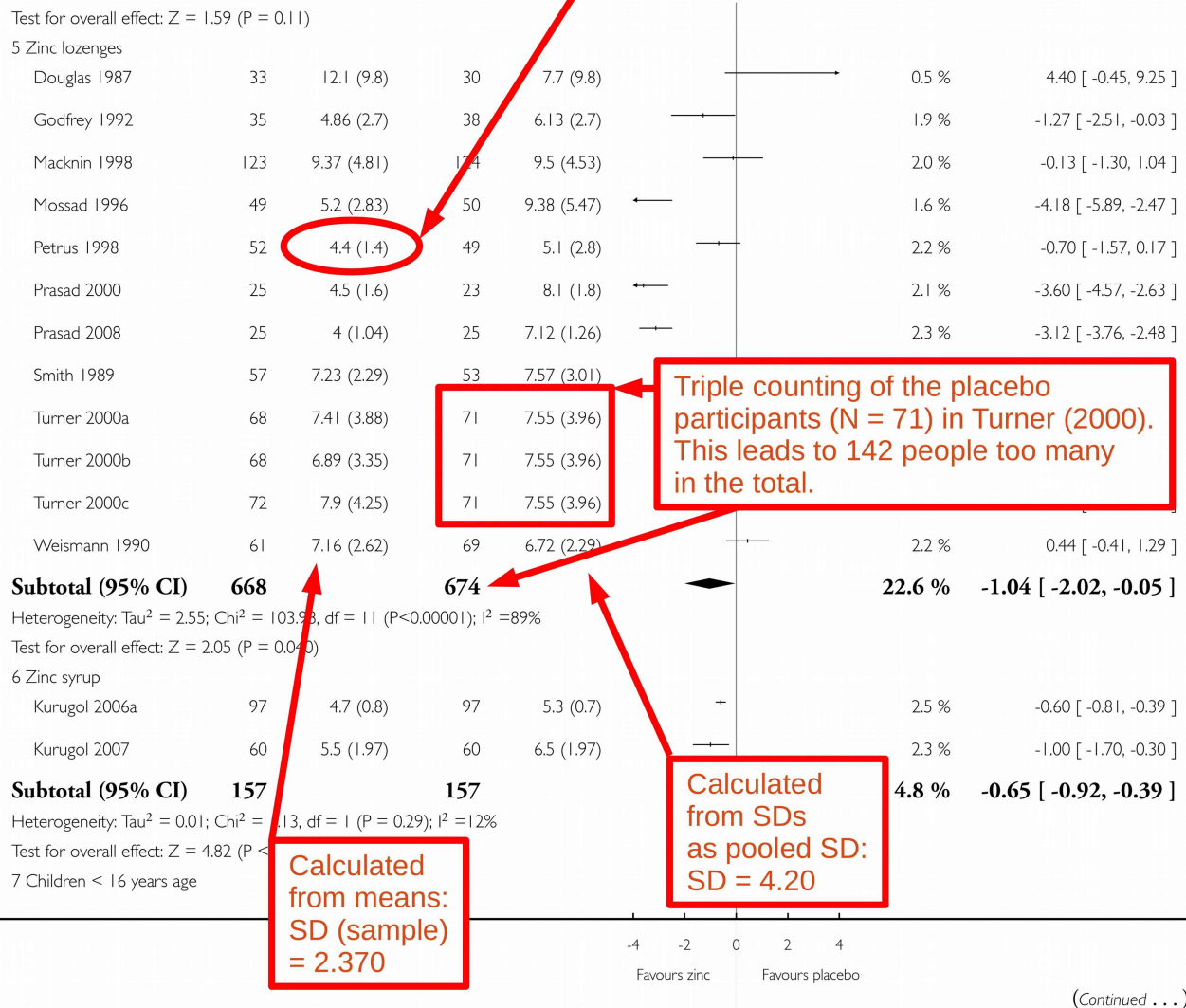
The two errors described above cause that the published unweighed mean values (6.75 and 7.5 days) and the estimate of the effect of zinc lozenges (1.04 days) are all wrong. Furthermore, the approach of calculating the unweighed mean duration of colds in the zinc and placebo groups in the Table suffers from the problem D) described on p. 9.

The SD calculated from the means of the zinc groups (the incorrect way) is 2.37 which is very close to the reported SD = 2.36, see p. 3. However for the placebo groups (see p. 3), the reported SD = 4.03 is not calculated from the means of the placebo groups. The pooled SD (PV 2015) for the placebo groups is 4.20 which is quite close to the reported SD = 4.03 and it is thus possible that the placebo SD is calculated from the SD values of the studies (the correct way).

Analyses 1.2.5 and 1.2.6 in the Cochrane review “zinc for the common cold” by Singh and Das (2013, p. 52)

At the foot of this page is a copy of the Table II of Petrus (1998)

In 2011, Hemilä wrote a Feedback (2011) to Singh and Das (2011), in which he pointed out that 4.4 days is **not** the zinc group mean. Instead, 4.4 days is the mean for the zinc and placebo groups combined. In Table II, Petrus reported the zinc group mean (SEM) as 3.8 (0.2) days, see the bottom of this page. Still, Singh and Das (2013) reiterate the wrong value of 4.4 days in the updated Cochrane review.



Zinc for the common cold (Review)

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Variable	Overall (n = 101) Mean (SEM)	Zinc (n = 52) Mean (SEM)	Placebo (n = 49) Mean (SEM)	t test*	df	P
Duration of all cold symptoms (days)	4.4 (0.2)	3.8 (0.2)	5.1 (0.4)	-2.7	73.8†	0.008
Duration of longest-lasting cold symptom (days)	6.1 (0.3)	5.3 (0.4)	7.1 (0.6)	-2.7	82.2†	0.009
Mean severity rating‡ (all symptoms)	1.45 (0.03)	1.41 (0.04)	1.50 (0.04)	-1.4	99	0.161

SEM = standard error of the mean.

* Independent groups *t* tests were used to determine whether differences existed between the zinc and placebo group means.

† Results using estimates assuming unequal group variances.

‡ Symptom severity rating scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe.

Calculation of the adverse events in the zinc lozenge studies by Das and Singh (2014)

The bold figures are those reported in the JAMA Synopsis by Das and Singh (2014). However, the reported mean rate of adverse events of 36.4% is based on counting the Turner (2000) placebo group data 3 times by Das and Singh (2014). Counting the Turner (2000) placebo group just once (the correct way) leads to placebo group mean rate of adverse events of 48.4%, which is marked by yellow.

Reproducing the rate of adverse events caused by zinc lozenges in the JAMA synopsis by Das and Singh (2014)

Analysis 2.12 of Singh and Das (2013)				
	Study	No. of participants	No. of any adverse events	Proportion with adverse events
Zinc lozenges	Macknin (1998)	123	106	86%
	Mossad (1996)	49	44	90%
	Turner (2000a)	68	11	16%
	Turner (2000b)	68	9	13%
	Turner (2000c)	72	14	19%
	Weismann (1990)	61	21	34%
	Total:	441	205	
	Ratio of total events per total participants:		46.5%	
Placebo	Macknin (1998)	124	99	80%
	Mossad (1996)	50	31	62%
	Turner (2000)	71	7	10%
	Second counting: Turner (2000)	71	7	10%
	Third counting: Turner (2000)	71	7	10%
	Weismann (1990)	69	15	22%
Counting the Turner (2000) placebo group 3 times (Das and Singh 2014):	Total:	456	166	
	Ratio of total events per total participants:		36.4%	
Counting the Turner (2000) placebo group only once (the correct way):	Total:	314	152	
	Ratio of total events per total participants:		48.4%	

5. Calculation of the rate of adverse events in the zinc lozenge studies

In the text section of the JAMA Synopsis, Das and Singh (2014, p. 1440) report on the adverse events caused by zinc lozenges as follows:

“Zinc lozenges were associated with a higher incidence of adverse events compared with placebo (46.5% for lozenges vs 36.4% for placebo; number needed to harm [NNH], 10).”

The percentages of adverse events are not reported in the Cochrane review by Singh and Das (2013). The data for the above percentages, however, can be traced to Analysis 2.12 of the Cochrane review by Singh and Das (2013, p. 65), see the previous page for the data extracted from that analysis.

In the Cochrane review by Singh and Das (2013) there were 12 zinc lozenge studies, but the analysis of adverse events is based on just 6 studies. In the JAMA Synopsis, Das and Singh (2014) calculated the mean rate of adverse events as follows. All participants in the 6 studies were summed, and all adverse events in the 6 studies were summed. Thereafter, the total sum of adverse events were divided by the total number of participants to obtain the mean rate of adverse events, which was published by Das and Singh (2014). A similar calculation was done for both the zinc and the placebo groups. This calculation is shown on the previous page, with bold type indicating the figures published by Das and Singh (2014).

In the 3 zinc lozenge groups reported by Turner (2000), the rate of adverse events varied from 13% to 19%, whereas in the Macknin (1998) study the rate was as high as 86%. The rate of adverse events in the placebo groups varied similarly from 10% in the Turner (2000) study to 80% in the Macknin (1998) study.

The analysis of adverse events reported in the JAMA Synopsis by Das and Singh (2014) has statistical problems and problems related to the compositions of lozenges.

First, here again Das and Singh (2014) counted the placebo group of Turner (2000) three times. If the triple counting is corrected by counting just once, the total number of placebo participants in the remaining 4 studies is 314, and they had 152 adverse events, which gives mean rate of adverse events in the placebo groups of 48.4%, see the previous page. This rate is 12 percentage points higher than the mean rate (36.4%) calculated for placebo groups in the JAMA Synopsis, see above. The corrected placebo rate is even slightly higher than the rate of 46.5% that was calculated for the zinc groups, see above. Thus, the 10% higher rate of adverse events in the zinc lozenge groups, reported by Das and Singh (2014), is a statistical artefact caused by the triple counting of the single placebo group of Turner (2000). Consequently, the NNH reported by Das and Singh (2014) is also incorrect.

Second, when there is such a dramatic variation in the adverse events from 10% to 80% in the placebo groups, and a similar variation for the zinc groups, it seems obvious that there cannot be a uniform rate of adverse events that is valid for all conditions. For example, comparison of the rates of the adverse events in the placebo groups reported by the Turner (2000) study (10%; 7/71) and the Macknin (1998) study (80%; 99/124) gives $P = 10^{-15}$ difference as calculated by using the Fisher exact test. Thus, random variation is not a credible explanation for such huge differences in rates of adverse events, and it is not reasonable to combine such inconsistent rates.

Some probable factors for the great variations in the rate of adverse events are the differences in definitions of adverse events, and the differences in the recording and reporting practices of adverse events between studies. Furthermore, even if an identical definition for adverse events was used,

it is highly plausible that some population groups report adverse events more sensitively than other population groups and this depends on gender, age, education, etc. Therefore, statistically the most reasonable approach is first to calculate the difference between zinc and placebo groups for each study, and thereafter pool the estimates by standard meta-analysis methods. Such an approach adjusts for the baseline variations in the rates of adverse events. The calculation method used by Das and Singh (2014) does not adjust for the baseline variations.

Furthermore, given that 3 studies on high dose zinc lozenges (Petrus 1998, Prasad 2000, Prasad 2008) had an average 42% reduction in the duration of common cold (Hemilä 2011, 2015), the most relevant question is: Do high dose zinc acetate lozenges cause adverse effects? The analysis by Das and Singh (2014) did not include any one of these 3 high dose zinc acetate lozenge studies.

Macknin (1998), Mossad (1996), Turner (2000a) and Weismann (1990) used lozenges made of zinc gluconate, see p. 16. Some types of zinc gluconate lozenges end up tasting bad after storage, but zinc acetate does not have such a problem, see Eby (2004, p. 34-35):

“Taste problems and oral irritation using zinc gluconate (ZG) caused most if not all of the problems found in commercializing zinc lozenges for colds. To reduce or eliminate the ZG/dextrose reaction and oral irritation, some manufacturers either used low amounts of ZG or added strong zinc binding agents, which reduced or eliminated efficacy. Although pure ZG is bland and chalky in taste, it reacts with dextrose and related carbohydrates (excluding fructose) upon aging of lozenge compositions to produce noisome bitterness and compliance-related inefficacy. ZG releases large amounts of neutrally charged hydroxide species likely to cross cell membranes and causes oral irritation. Bitterness occurs in all ZG lozenges except those that either do not contain carbohydrates (excluding fructose), or that contain strong extramolar zinc binding agents, which results in something other than ZG. For these reasons, ZG is no longer believed suitable for use in zinc lozenges for treating colds.

On the other hand, zinc acetate allows the production of pleasant tasting, flavor stable lozenges releasing large amounts of iZn [free zinc ions] either in hard candies or compressed tablets without flavor or stability issues. The mouth-feel produced is sufficiently like the mouth-feel of tea (slight astringency) to allow using tannic acid without added bitter agents as a placebo in clinical trials.”

None of the high dose zinc acetate lozenge trials (Petrus 1998, Prasad 2000, Prasad 2008) reported bad taste to be a problem and there was no substantial difference between the zinc and placebo groups in the recorded adverse effects, and only a few drop-outs occurred. For example, the most recent of these studies, Prasad (2008) reported in Table 3 of their publication that a sour taste was more common in the zinc group (7/25 vs. 2/25, though $P = 0.13$ for the difference) whereas nausea (3 vs 1) or constipation (2 vs 1) and diarrhea (1 vs 1) did not differ considerably between groups. Thus, the high dose zinc acetate lozenge did not seem to cause harm, either as bad taste or within the GI region. Furthermore, when a common cold patient experiences acute adverse effects such as bad taste, the particular patient can simply stop taking the zinc acetate lozenges.

Given that the strongest evidence of benefit is found for high dose zinc acetate lozenges, the possible bad taste of zinc gluconate lozenges is not a relevant issue. In particular, the bad taste of some zinc gluconate lozenges cannot be extrapolated to infer bad taste of the zinc acetate lozenges.

Thus, the 10 percentage point difference in adverse events between zinc lozenge and placebo groups that was calculated by Das and Singh (2014) can be explained by the triple counting of the Turner (2000) placebo group. Furthermore, summing all adverse events and dividing by all participants as was done by Das and Singh (2014) is statistically unsound. Finally, even if the analysis of adverse events had no such statistical problems, it would still be uninformative about the adverse events of high dose zinc acetate lozenges, for which there is compelling evidence of effectiveness (Hemilä 2011, 2015).

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